IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lorraine Elisabeth Pena and
Maw-Sheng Wu

Confirmation No.: 5718

Application No.: 09/634,399

Group Art Unit: 1617

Filing Date: August 9, 2000

Examiner: S. Kantamneni

For: NOVEL COMPOSITIONS OF MINOXIDIL

Assistant Commissioner for Patents
Washington DC 20231

Sir:

SUPPLEMENTAL DECLARATION OF LORRAINE E. PENA

UNDER 37 C.F.R. § 1.132

I, Lorraine E. Pena, Ph.D., hereby declare the following:

(1) I received my Bachelor of Science Degree in Chemistry and German from the University of Missouri-Kansas City in 1975. I received my Ph.D. degree in Pharmacy from the same university in 1980.

(2) I have extensive experience in the field of pharmaceutical formulation chemistry and have been extensively involved during the past 24 years in the development of pharmaceutical compositions for topical applications. In particular, I have had extensive experience in the preparation of pharmaceutical compositions containing minoxidil for topical applications.

(3) I am employed as an Associate Research Fellow at what has recently become known as Pfizer Inc. (previously Pharmacia Corporation, to whom the present application was originally assigned). As set forth in my *curriculum vitae*, a copy of which was submitted with the previous Declaration that I executed on October 11, 2004, I have been associated

with Pharmacia Corporation or its predecessors in interest, since 1980. My further experience and qualifications, including my patents and publications, are also set forth in my *curriculum vitae*.

(4) I am a joint inventor of the subject matter claimed in the above-identified application, and have studied and am familiar with the Examiner's Office Action dated July 14, 2004, and the references cited therein, including, in particular, Preuilh et al., U.S. Patent No. 6,106,848 (hereinafter "Preuilh"), Ewers et al, WO 97/03709 (translation, hereinafter "Ewers"), and Pena, U.S. Patent No. 5,225,189 (hereinafter "Pena"). With regard to the Pena patent, I am the sole inventor of the subject matter claimed therein.

(5) Independent Claim 1 in the present application defines single-phase gel compositions comprising from greater than about 5% to about 8% minoxidil, a thickening agent, and a pharmaceutically acceptable solvent, in which the minoxidil is completely solubilized in the composition. The thickening agent in Claim 1 is defined as being a crosslinked copolymer of acrylic acid. Since the term "carbomer," as defined in the present application, refers to high molecular weight crosslinked *homopolymers* of acrylic acid, a person of ordinary skill in the art would readily recognize that the crosslinked acrylic acid copolymers recited in Claim 1 are "non-carbomeric."

Independent Claim 36 defines single-phase gels that comprise from about 5% to about 8% minoxidil, greater than 50% of a pharmaceutically acceptable solvent, and up to 25% water. The compositions defined by this claim are thickened with a solvent-tolerant carbomer, such as, for example, Carbopol7 UltrezJ 10. As with the compositions defined in Claim 1, the minoxidil is completely solubilized in the claimed compositions.

Independent Claim 62 defines single-phase gel compositions comprising greater than about 5% to about 8% minoxidil, together with specified amounts of a polyol, an alcohol, a crosslinked copolymer of acrylic acid, and a sufficient quantity of water. A neutralizing

agent may also be present, in concentrations of up to 3%. As with the compositions defined in the other independent claims, Claim 62 recites that the minoxidil is completely solubilized in the claimed compositions.

(6) The Office Action dated July 14, 2004 alleges that the then-pending claims were obvious, and therefore unpatentable. The teachings of Preuilh, together with Ewers and Pena, were combined to reject many of the claims. Additional references, including Samour, U.S. Patent No. 5,620,980, Sine et al., U.S. Patent No. 6,423,329, Anton et al., U.S. Patent No. 5,798,426 and Grollier, GB 2194887, were added in rejections directed to the remaining claims. All of the rejections were derived from that based on Prueilh, in view of Ewers and Pena, however.

(7) I addressed the rejections set forth in the July 14, 2004 Office Action in my previous Declaration, which I executed on October 11, 2004. I now wish to supplement that declaration, to the extent that the previous rejections may be maintained with regard to the claims, as presently amended.

(8) Preuilh is directed to oil-in-water emulsions that contain, in addition to the oil (fatty phase) and water (aqueous phase), 30% to 50% of a pro-penetrating glycol, an emulsifying agent and a biologically active agent. A laundry-list of biologically active agents, including minoxidil, is provided, and Preuilh indicates that the compositions can comprise from 0.0001% to 20% by weight of the active agent. Preuilh further teaches that a polymeric emulsifier, such as Pemulen TR1, Pemulen TR2, Carbopol 1342 or Carbopol 1382, may be used as the emulsifying agent to stabilize the disclosed emulsions. Preuilh also states that a gelling or thickening agent, such as hydroxypropylcellulose, or a carbomer, such as Carbopol 910 or 934, can further be included to thicken the emulsion. A single example of

an exemplary emulsion is set forth in Preuilh in Example 1. This example utilizes Pemulen TR2 as an emulsifier. Hydroxyproylmethylcellulose is used as a thickening (gelling) agent.

(9) Preuilh clearly does not teach or suggest the compositions claimed in the present application. In this regard, the present claims distinguish fundamentally over the Preuilh patent in that Preuilh is directed solely to the preparation of biphasic emulsions in which an oil (or fatty) phase is dispersed in a water (or aqueous) phase. In contrast, the presently claimed compositions are single-phase gels, *i.e.*, semisolids which comprise organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. There is no oil (fatty) phase in the single-phase gels of the present invention.

(10) The present claims further define over the Preuilh patent in that Preuilh fails to disclose or suggest thickening agents in the form of crosslinked copolymers of acrylic acid, such as acrylate/C_{10-30} alkyl acrylate crosspolymers, or solvent-tolerant carbomers, such as Carbopol® Ultrez™ 10. Although Preuilh suggests that acrylate/C_{10-30} alkyl acrylate crosspolymers may be employed in the disclosed compositions, such crosspolymers are used to emulsify the oil phase in the water phase. Single-phase gels such as those defined in the present claims are not composed of immiscible phases, and therefore the use of an emulsifier is generally unwarranted. Thus, should one of ordinary skill in the art looking to prepare a single-phase gel composition come upon the Preuilh patent, he or she would not be motivated to employ any of the teachings therein, including the use of agents to emulsify immisicible phases, as described in Preuilh.

(11) Moreover, although Preuilh includes minoxidil in a laundry list of suitable biologically active agents, the reference provides no examples of any minoxidil-containing compositions. As reported in my previous declaration, efforts to apply the teachings in the

Preuilh patent, including the preparation of a 3% minoxidil preparation in accordance with Preuilh, were unsuccessful, as the resulting composition proved to be unstable, and the oil phase and aqueous phase separated when the composition was allowed to sit overnight. On the basis of this test work, I concluded that Preuilh does not describe a stable, pharmaceutically elegant emulsion containing 3% minoxidil, as was asserted in the Office Action. I believe that compositions having even greater instability would result if the test work was repeated with higher concentrations of minoxidil, such as from about 5% to about 8% minoxidil, as recited in the presently amended claims.

(12) Since the test work reported in my previous declaration demonstrated that the compositions taught by Preuilh are unstable when prepared with higher concentrations of minoxidil (such as are recited in the instant claims), it is my opinion that this reference is completely irrelevant to the claimed invention. It is further my opinion that an ordinarily skilled artisan would also consider Preuilh irrelevant to the presently claimed invention.

(13) The Office Action combines Preuilh with Ewers and Pena, stating that it would have been obvious to one of ordinary skill in the art to prepare the minoxidil emulsions described by Preuilh in the form of single phase gels, because Pena describes single-phase minoxidil gel formulations, and Ewers teaches that gelled emulsions and single-phase gels are interchangeable forms for any transdermal application.

(14) It is my opinion that the assertion in the Office Action that gelled emulsions and single-phase gels are generally interchangeable forms for transdermal applications of biologically active materials is incorrect. One of ordinary skill in the art would readily understand that while a given drug may be prepared in any number of formulations for delivery, different vehicles and delivery forms may lead to drastically different bioavailability

and therapeutic effect. A basic text regarding pharmaceutical formulations such as *Remington's Pharmaceutical Sciences*, for example, states that

> In the formulation of a vehicle for topical drug application many factors must be considered. Drug stability, specific product use, site of application and product type must be combined in a dosage form which will readily release the drug when placed in contact with the skin. A vehicle optimized for delivery of hydrocortisone may be quite inappropriate for delivery of a different steroid.[1]

Thus, *Remington's* teaches that even within a given class of compounds (*i.e.*, steroids), different individual members may require completely different vehicles for topical application. Contrary to the assertions in the Office Action, a person of ordinary skill in the art therefore would *not* conclude that a vehicle useful for the delivery of an estrogen (as is the subject of the Ewers reference) would also be useful for the delivery of a completely different compound, such as minoxidil. While Ewers may teach that the particular estrogen that is the subject of that application may be prepared as either a gelled emulsion or as a single-phase gel, any assertion that the two delivery forms are generally interchangeable is simply incorrect, as would be readily understood by the ordinarily skilled artisan. Accordingly, it is my opinion that an ordinarily skilled artisan would also consider Ewers to be irrelevant to the instant invention.

(15) Pena describes single-phase minoxidil gels, and provides examples of gels containing up to 3% minoxidil that are thickened with the carbomer Carbopol®934P. Carbopol®934P is not a crosslinked copolymer of acrylic acid, and does not meet the definition of "solvent-tolerant carbomer" set forth in the present application. Example IV of the present application describes a failed effort to prepare a 5% minoxidil gel using Carbopol®934P. Thus, although Pena suggests that single-phase minoxidil gels may be

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[1] *See*, Block, LH, "Medicated Applications," *Remington's Pharmaceutical Sciences, 18th Ed.,* (Gennaro, AR, Ed.), page 1600 (Philadelphia College of Pharmacy and Science, 1990) (attached hereto as Exhibit 1).

prepared using the carbomer Carbopol®934P, it does not teach how to make such gels containing higher concentrations of minoxidil, such as from about 5% to about 8% minoxidil as recited in the presently amended claims, nor does it suggest the use of either solvent-tolerant carbomers or crosslinked copolymers of acrylic acid to produce such compositions.

(16) It is thus my conclusion that the cited references fail to teach or suggest the present invention, as defined by the presently amended claims. One of ordinary skill in the art would neither be motivated to combine the cited references as set forth in the Office Action dated July 14, 2004, nor would the references, either alone or in combination, enable one of ordinary skill in the art to prepare the compositions defined by the claims.

(17) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11 April 2005

Lorraine E. Pena

Lorraine E. Pena, Ph.D